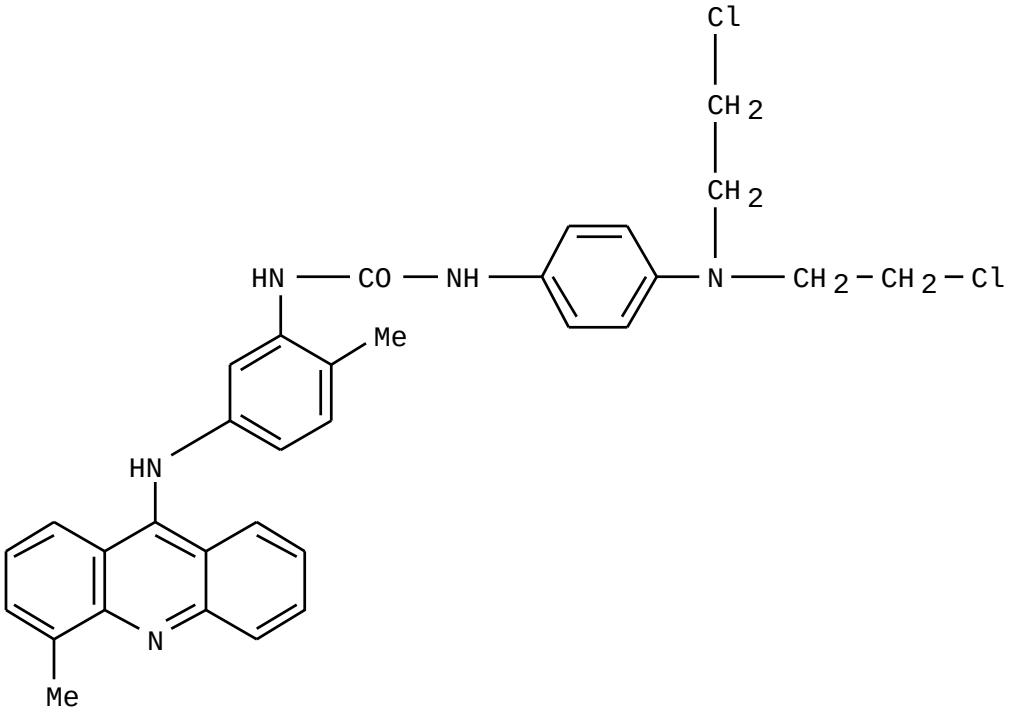
Answer 1:

Bibliographic Information

Synthesis and biological activity of stable and potent antitumor agents, aniline nitrogen mustards linked to 9-anilinoacridines via a urea linkage. Kapuriya, Naval; Kapuriya, Kalpana; Zhang, Xiuguo; Chou, Ting-Chao; Kakadiya, Rajesh; Wu, Yu-Tse; Tsai, Tung-Hu; Chen, Yu-Ting; Lee, Te-Chang; Shah, Anamik; Naliapara, Yogesh; Su, Tsann-Long. Institute of Biomedical Sciences, Laboratory of Bioorganic Chemistry, Academia Sinica, Taipei, Taiwan. Bioorganic & Medicinal Chemistry (2008), 16(10), 5413-5423. Publisher: Elsevier Ltd., CODEN: BMECEP ISSN: 0968-0896. Journal written in English. CAN 149:118685 AN 2008:642488 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To improve the chem. stability and therapeutic efficacy of N-mustard, a series of Ph N-mustard linked to DNA-affinic 9-anilinoacridines and acridine via a urea linker were synthesized and evaluated for antitumor studies. The new N-mustard derivs. were prepd. by the reaction of 4-bis(2-chloroethyl)aminophenyl isocyanate with a variety of 9-anilinoacridines or 9-aminoacridine. The antitumor studies revealed that these agents exhibited potent cytotoxicity in vitro without cross-resistance to taxol or vinblastine and showed potent antitumor therapeutic efficacy in nude mice against human tumor xenografts. It also showed that 24d (I) was capable of inducing marked dose-dependent levels of DNA crosslinking by comet assay and has long half-life in rat plasma.



I

Answer 2:

Bibliographic Information

Mechanism of Action and Preclinical Antitumor Activity of the Novel Hypoxia-Activated DNA Cross-Linking Agent PR-104.

Patterson, Adam V.; Ferry, Dianne M.; Edmunds, Shelley J.; Gu, Yongchuan; Singleton, Rachelle S.; Patel, Kashyap; Pullen, Susan M.; Hicks, Kevin O.; Syddall, Sophie P.; Atwell, Graham J.; Yang, Shangjin; Denny, William A.; Wilson, William R. Auckland Cancer Society Research Centre, School of Medical Sciences, University of Auckland, Auckland, N. Z. Clinical Cancer Research (2007), 13(13), 3922-3932. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:534141 AN 2007:718552 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Hypoxia is a characteristic of solid tumors and a potentially important therapeutic target. Here, we characterize the mechanism of action and preclin. antitumor activity of a novel hypoxia-activated prodrug, the 3,5-dinitrobenzamide nitrogen mustard PR-104, which has recently entered clin. trials. Exptl. Design: Cytotoxicity in vitro was evaluated using 10 human tumor cell lines. SiHa cells were used to characterize metab. under hypoxia, by liq. chromatog.-mass spectrometry, and DNA damage by comet assay and γH2AX formation. Antitumor activity was evaluated in multiple xenograft models (PR-104 ± radiation or chemotherapy) by clonogenic assay 18 h after treatment or by tumor growth delay. RESULTS: The phosphate ester "pre-prodrug" PR-104 was well tolerated in mice and converted rapidly to the corresponding prodrug PR-104A. The cytotoxicity of PR-104A was increased 10- to 100-fold by hypoxia in vitro. Redn. to the major intracellular metabolite, hydroxylamine PR-104H, resulted in DNA crosslinking selectively under hypoxia. Reaction of PR-104H with chloride ion gave lipophilic cytotoxic metabolites potentially able to provide bystander effects. In tumor excision assays, PR-104 provided greater killing of hypoxic (radioresistant) and aerobic cells in xenografts (HT29, SiHa, and H460) than tirapazamine or conventional mustards at equiv. host toxicity. PR-104 showed single-agent activity in six of eight xenograft models and greater than additive antitumor activity in combination with drugs likely to spare hypoxic cells (gemcitabine with Panc-01 pancreatic tumors and docetaxel with 22RV1 prostate tumors). CONCLUSIONS: PR-104 is a novel hypoxia-activated DNA crosslinking agent with marked activity against human tumor xenografts, both as monotherapy and combined with radiotherapy and chemotherapy.

Answer 3:

Bibliographic Information

Therapeutic Effects of Monoclonal Antibody-β-Lactamase Conjugates in Combination with a Nitrogen Mustard Anticancer Prodrug in Models of Human Renal Cell Carcinoma. Svensson, Haakan P.; Frank, Ian S.; Berry, Karen K.; Senter, Peter D. Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA, USA. Journal of Medicinal Chemistry (1998), 41(9), 1507-1512. Publisher: American Chemical Society, CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 128:278707 AN 1998:275198 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A panel of 13 renal cell carcinoma cell lines was evaluated for the expression of antigens recognized by the L6 and L49 monoclonal antibodies. All of the cell lines were strongly pos. for the L6 antigen, and 9/13 bound 96.5, which, like the L49 monoclonal antibody, recognizes the p97 melanotransferrin antigen. The L6 and L49 antibodies were chem. conjugated to Enterobacter cloacae β-lactamase (bL), and their abilities to effect site-selective anticancer prodrug activation on two of the renal cell carcinoma cell lines (SN12P and 1934J) were evaluated in vitro and in vivo. L49-bL was 10-90-fold more potent in vitro than L6-bL for the activation of 7-(4-carboxybutanamido)cephalosporin mustard (CCM), a cephalosporin prodrug of phenylenediamine mustard (PDM). In addn., L49-bL showed higher degrees of specific SN12P and 1934J intratumoral uptake than L6-bL, even though the expression of L6 antigen was 2-fold higher than that of p97. These differences might be due to the high-affinity antigen binding of L49-bL relative to L6-bL. In vivo studies utilizing nude mice with established s.c. SN12P and 1934J tumor xenografts demonstrated that L49-bL/CCM combinations led to regressions and cures at well-tolerated doses, while L6-bL/CCM and the nonbinding control conjugate P1.17-bL in combination with CCM were ineffective. Conjugate localization in 1934J tumors was much lower than that obsd. in SN12P tumors, a finding that might account for the higher activities of L49-bL/CCM in the latter model. These data show that the p97 antigen on renal cell carcinomas can be exploited for selective prodrug activation, even on tumors that localize very small amts. of the L49-bL conjugate.

Answer 4:

Bibliographic Information

Activation of anticancer prodrugs by monoclonal antibodyenzyme conjugates. Senter, Peter D.; Kerr, David E.; Schreiber, George S.; Vrudhula, Vivekinanda M.; Svensson, Hakan P. Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA, USA. Book of Abstracts, 210th ACS National Meeting, Chicago, IL, August 20-24 (1995), (Pt. 2), NUCL-010. Publisher: American Chemical Society, Washington, D. C CODEN: 61XGAC Conference; Meeting Abstract written in English. AN 1995:924531 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A strategy for the delivery of cytotoxic agents to solid tumors is described in which monoclonal antibodies are used as carriers for enzymes to tumor cell surfaces. The enzymes are chosen for their abilities to convert relatively noncytotoxic drug precursors (prodrugs) into active anticancer drugs. The drugs thus formed can then penetrate into nearby tumor cells, resulting in cell death. Many enzymes have been explored in this drug targeting strategy. Of them, β-lactamases have shown particular promise because of their high activities and abilities to activate a wide variety of cephalosporin contg. anticancer prodrugs. We show that monoclonal antibody-β-lactamase conjugates activate nitrogen mustard and anthracyclin prodrugs, leading to regressions and cures of established human tumor xenografts in nude mice. The scope of the methodol. and a mechanistic basis for activity will be described.

Answer 5:

Bibliographic Information

Compounds with antiblastic activity. XLI. Synthesis of new nitrogen mustards related to N,N-bis(β-chloroethyl)aniline. Artico, M.; Filacchioni, G.; Vomero, S. Ist. Chim. Farm. Tossicol., Univ. Roma, Rome, Italy. Farmaco, Edizione Scientifica (1971), 26(9), 805-11. CODEN: FRPSAX ISSN: 0430-0920. Journal written in Italian. CAN 76:3772 AN 1972:3772 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Schiff bases (I, R = H, OMe, OEt; R1 = H, OH, CH2OH, CO2H; R2 = H, Cl, Me, CO2H; R3 = H, OH, NO2, CO2H) were prepd. by condensation of equimol. amts. of appropriate aryl aldehyde nitrogen mustards and suitably substituted anilines in a min. amt. of boiling anhyd. alc. Selected I were reduced to the related dihydro derivs. by hydrogenation in EtOAc in the presence of 10 Pd-C, but mostly only unworkable mixts. were obtained. Suitable I (R = H, OMe, OEt; R1 = CH2OH, CO2H; R2 = H; R3 = H, NO2) were transformed into the corresponding 3,1-benzoxazines (II, R = H, OMe, OEt; R2 = H, NO2; Y = CH2, CO) by refluxing 4.5 hr in Ac2O. None of the compds. showed promising antitumor activity when tested against Ehrlich carcinoma in the mouse, lymphocytic leukemia L 1210, or human heterotransplanted carcinoma GW 77 in the hamster.

Answer 6:

Bibliographic Information

The nitroreductase prodrug SN 28343 enhances the potency of systemically administered armed oncolytic adenovirus ONYX-411(NTR). Singleton D C; Li D; Bai S Y; Syddall S P; Smaill J B; Shen Y; Denny W A; Wilson W R; Patterson A V Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand Cancer gene therapy (2007), 14(12), 953-67. Journal code: 9432230. E-ISSN:1476-5500. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17975564 AN 2007676732 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Conditionally replicating adenoviruses (CRAd) 'armed' with prodrug-activating genes have the potential to augment the efficacy of virotherapy. An Escherichia coli nitroreductase (NTR) gene (nfsB) was introduced into the E3B region of the

systemically active CRAd ONYX-411, to produce ONYX-411(NTR), which had single agent oncolytic activity equivalent to unarmed virus in vitro and in vivo. A fluorogenic probe (SN 29884) developed to monitor NTR expression revealed robust, durable NTR expression in ONYX-411(NTR) infected neoplastic but not primary human cell lines. NTR expression occurred >24 h post-infection in parallel with fiber and was sensitive to ara-C indicating transcriptional linkage to viral replication. A novel NTR prodrug, the 3,5-dinitrobenzamide-2-bromomustard SN 27686, was shown to be more dose potent and selective than CB 1954 and provided a superior bystander effect in 3D multicellular layer cultures. Its water-soluble phosphate ester SN 28343 was substantially more active than CB 1954 against xenografts containing a minority of stable NTR-expressing cells. A single intravenous dose of ONYX-411(NTR) (10(8) PFU) to nude mice bearing large H1299 xenografts (>350 mm(3)) resulted in tumor-specific NTR expression which increased over time. Despite extensive viral spread by day 14, this conservative virus dose and schedule was unable to control such well-established tumors. However, subsequent administration of SN 28343 resulted in the majority of mice (62.5%) being tumor-free on day 120.

Answer 7:

Bibliographic Information

Oxygen dependence and extravascular transport of hypoxia-activated prodrugs: comparison of the dinitrobenzamide mustard PR-104A and tirapazamine. Hicks Kevin O; Myint Hilary; Patterson Adam V; Pruijn Frederik B; Siim Bronwyn G; Patel Kashyap; Wilson William R Auckland Cancer Society Research Centre, University of Auckland School of Medical Sciences, Auckland, New Zealand. k.hicks@auckland.ac.nz International journal of radiation oncology, biology, physics (2007), 69(2), 560-71. Journal code: 7603616. ISSN:0360-3016. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17869669 AN 2007553278 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: To compare oxygen dependence and tissue transport properties of a new hypoxia-activated prodrug, PR-104A, with tirapazamine, and to evaluate the implications for antitumor activity when combined with radiotherapy. METHODS AND MATERIALS: Oxygen dependence of cytotoxicity was measured by clonogenic assay in SiHa cell suspensions. Tissue transport parameters were determined using SiHa multicellular layers. Spatially resolved pharmacokinetic (PK) and pharmacodynamic (PD) models were developed to predict cell killing in SiHa tumors and tested by clonogenic assay 18 h after treatment with the corresponding phosphate ester, PR-104. RESULTS: The K-value (oxygen concentration to halve cytotoxic potency) of PR-104A was 0.126 +/- 0.021 microM (10-fold lower than tirapazamine at 1.30 +/- 0.28 microM). The diffusion coefficient of PR-104A in multicellular layers (4.42 +/- 0.15 x 10(-7) cm2 s(-1)) was lower than that of tirapazamine (1.30 +/- 0.05 x 10(-6) cm2 s(-1)) but PK modeling predicted better penetration to hypoxic cells in tumors because of its slower metabolism. The tirapazamine PK/PD model successfully predicted the measured activity in combination with single-dose radiation against SiHa tumors, and the PR-104A model underpredicted the activity, which was greater for PR-104 than for tirapazamine (at equivalent host toxicity) both with radiation and as a single agent. CONCLUSION: PR-104/PR-104A has different PK/PD properties from tirapazamine and superior activity with single-dose radiotherapy against SiHa xenografts. We have inferred that PR-104A is better able to kill cells at intermediate partial pressure of oxygen in tumors than implied by the PK/PD model, most likely because of a bystander effect resulting from diffusion of its activated metabolites from severely hypoxic zones.

Answer 8:

Bibliographic Information

Analysis of the hypoxia-activated dinitrobenzamide mustard phosphate pre-prodrug PR-104 and its alcohol metabolite PR-104A in plasma and tissues by liquid chromatography-mass spectrometry. Patel Kashyap; Lewiston David; Gu Yongchuan; Hicks Kevin O; Wilson William R Auckland Cancer Society Research Centre, University of Auckland, Private Bag 92019, Auckland, New Zealand Journal of chromatography. B, Analytical technologies in the biomedical and life sciences (2007), 856(1-2), 302-11. Journal code: 101139554. ISSN:1570-0232.

Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (VALIDATION STUDIES) written in English. PubMed ID 17644498 AN 2007509991 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PR-104 is a dinitrobenzamide mustard pre-prodrug that is activated by reduction to a cytotoxic hydroxylamine metabolite in hypoxic tumour cells; it has recently commenced Phase I clinical trial. Here, we report two validated methods for the determination of PR-104 and its alcohol hydrolysis product, PR-104A in plasma and tissues across species. A high pH LC/MS/MS method was optimised for rapid and sensitive analysis of both analytes in rat, dog and human plasma. This assay was linear over the concentration range 0.005-2.5 microg/ml for PR-104 and 0.05-25 microg/ml for PR-104A (0.005-2.5 microg/ml for rat). A second method, using a low pH LC separation, was designed to provide higher chromatographic resolution, facilitating identification of metabolites. Both methods were successfully applied to the plasma pharmacokinetics of PR-104 and PR-104A in rats. In addition, cytotoxic reduced metabolites of PR-104A were identified in human tumour xenografts by the higher chromatographic resolution method.

Answer 9:

Bibliographic Information

Suicide gene therapy of human colon carcinoma xenografts using an armed oncolytic adenovirus expressing carboxypeptidase G2. Schepelmann Silke; Ogilvie Lesley M; Hedley Douglas; Friedlos Frank; Martin Janet; Scanlon Ian; Chen Ping; Marais Richard; Springer Caroline J The Institute of Cancer Research, Cancer Research UK Centres for Cancer Therapeutics, London, United Kingdom Cancer research (2007), 67(10), 4949-55. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17510425 AN 2007298574 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We have designed a targeted systemic suicide gene therapy that combines the advantages of tumor-selective gene expression, using the human telomerase promoter (hTERT), with the beneficial effects of an oncolytic adenovirus to deliver the gene for the prodrug-activating enzyme carboxypeptidase G2 (CPG2) to tumors. Following delivery of the vector (AdV.hTERT-CPG2) and expression of CPG2 in cancer cells, the prodrug ZD2767P was administered for conversion by CPG2 to a cytotoxic drug. This system is sometimes termed gene-directed enzyme prodrug therapy (GDEPT). Here, we have shown that it is applicable to 10 human colorectal carcinoma cell lines with a direct correlation between viral toxicity and CPG2 production. SW620 xenografts were selected for analysis and were significantly reduced or eradicated after a single administration of AdV.hTERT-CPG2 followed by a prodrug course. The oncolytic effect of adenovirus alone did not result in DNA cross-links or apoptosis, whereas DNA cross-links and apoptosis occurred following prodrug administration, showing the combined beneficial effects of the GDEPT system. The apoptotic regions extended beyond the areas of CPG2 expression in the tumors, indicative of significant bystander effects in vivo. Higher concentrations of vector particles and CPG2 were found in the AdV.hTERT-CPG2 plus prodrug-treated tumors compared with the virus alone, showing an unexpected beneficial and cooperative effect between the vector and GDEPT. This is the first time that a tumor-selective GDEPT vector has been shown to be effective in colorectal carcinoma and that apoptosis and significant bystander effects have been identified as the mechanisms of cytotoxicity within the tumor.

Answer 10:

Bibliographic Information

Synthesis and structure-activity relationships for 2,4-dinitrobenzamide-5-mustards as prodrugs for the Escherichia coli nfsB nitroreductase in gene therapy. Atwell Graham J; Yang Shangjin; Pruijn Frederik B; Pullen

Susan M; Hogg Alison; Patterson Adam V; Wilson William R; Denny William A Auckland Cancer Society Research Centre, School of Medical Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
Journal of medicinal chemistry (2007), 50(6), 1197-212. Journal code: 9716531. ISSN:0022-2623. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17326614 AN 2007157441 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A series of 2,4-dinitrobenzamide mustards were prepared from 5-chloro-2,4-dinitrobenzoic acid or the corresponding 5-dimesylate mustard as potential prodrugs for gene-directed enzyme prodrug therapy (GDEPT) with the E. coli nfsB nitroreductase (NTR). The compounds, including 32 new examples, were evaluated in four pairs of NTR+ve/-ve cell lines for selective cytotoxicity (IC50 and IC50 ratios), in multicellular layer (MCL) cultures for bystander effects, and for in vivo activity against tumors grown from stably NTR transfected EMT6 and WiDr cells in nude mice. Multivariate regression analysis of the IC50 results was undertaken using a partial least-squares projection to latent structures model. In NTR-ve lines, cytotoxicity correlated positively with logP, negatively with hydrogen bond acceptors (HA) and donors (HD) in the amide side chain, and positively with the reactivity of the less-reactive leaving group of the mustard function, likely reflecting toxicity due to DNA monoadducts. Potency and selectivity for NTR+ve lines was increased by logP and HD, decreased by HA, and was positively correlated with the leaving group efficiency of the more-reactive group, likely reflecting DNA crosslinking. NTR selectivity was greatest for asymmetric chloro/mesylate and bromo/mesylate mustards. Bystander effects in the MCL assay also correlated positively with logP and negatively with leaving group reactivity, presumably reflecting the transcellular diffusion/reaction properties of the activated metabolites. A total of 18 of 22 mustards showed equal or greater bystander efficiencies in MCLs than the aziridinylbenzamide CB 1954, which is currently in clinical trial for NTR-GDEPT. The dibromo and bromomesylate mustards were surprisingly well tolerated in mice. High MTD/IC50 (NTR+ve) ratios translated into curative activity of several compounds against NTR+ve tumors. A bromomesylate mustard showed superior activity against WiDr tumors grown from 1:9 mixtures of NTR+ve and NTR-ve cells, indicating a strong bystander effect in vivo.

Answer 11:

Bibliographic Information

Antileukemic and cytogenetic activity by triple administration of three modified steroidal derivatives of nitrogen mustards. Fousteris M A; Papageorgiou A; Arsenou E S; Koutsourea A I; Karaberis E; Mourelatos D; Onyango D O; Nikolaropoulos S S Laboratory of Pharmaceutical Chemistry, School of Health Sciences, Department of Pharmacy, University of Patras, Rion, Greece Chemotherapy (2007), 53(2), 118-26. Journal code: 0144731. E-ISSN:1421-9794. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17308378 AN 2007141186 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Combination chemotherapy is widely and routinely used for most cancer patients. The main objective of this study is an effort to develop new anticancer drugs and procedures with enhanced antitumor activity and reduced toxicity. This study was designed to determine the antileukemic and cytogenetic activity of five mixtures of three specific steroidal esters of aromatic nitrogen mustards in different proportions. This is the next step of two previous studies where the combination of two such esteric analogues was investigated with promising results. All of the five mixtures used proved active against leukemia P388 and in the induction of sister chromatid exchanges, indicating that the combination of the same class of compounds can be successful, especially when a highly potent agent is combined with another less active but probably mechanistically supplementary one. These results can be used in future experiments in order to further scout the specific role of the steroidal part of these molecules in the antileukemic potency of them. Copyright 2007 S. Karger AG, Basel.

Answer 12:

Bibliographic Information

Hybrid aza-steroid alkylators in the treatment of colon cancer. Trafalis Dimitrios T P 1st Department of Medical Oncology, Metaxa Cancer Hospital, Piraeus, Greece. dtrafalis@yahoo.com <dtrafalis@yahoo.com> Cancer letters (2006), 243(2), 202-10. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16412564 AN 2006727060 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We tested two alkylating homo-aza-steroid esters, lactandrate and lactestoxate, for antineoplastic activity against colon adenocarcinoma in vitro and in vivo. Cytostatic and cytotoxic activity was evaluated in vitro with the SRB colormetric assay against nine human colon adenocarcinoma cell lines. The in vivo anti-tumour effect was determined against two rodent colon carcinomas, the Colon 26 and the relatively chemoresistant Colon 38 carcinoma, as well as against the human xenograft CX-1 colon carcinoma. Both of the tested compounds displayed a very satisfactory anti-cancer activity in vitro and in vivo. Lactestoxate produced a significantly higher overall activity than lactandrate.

Answer 13:

Bibliographic Information

Potent antitumor 9-anilinoacridines and acridines bearing an alkylating N-mustard residue on the acridine chromophore: synthesis and biological activity. Su Tsann-Long; Lin Yi-Wen; Chou Ting-Chao; Zhang Xiuguo; Bacherikov Valeriy A; Chen Ching-Huang; Liu Leroy F; Tsai Tsong-Jen Laboratory of Bioorganic Chemistry, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan. tlsu@ibms.sinica.edu.tw Journal of medicinal chemistry (2006), 49(12), 3710-8. Journal code: 9716531. ISSN:0022-2623. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16759114 AN 2006379451 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A series of 9-anilinoacridine and acridine derivatives bearing an alkylating N-mustard residue at C4 of the acridine chromophore were synthesized. The N-mustard pharmacophore was linked to the C4 of the acridine ring with an O-ethyl (O-C(2)), O-propyl (O-C(3)), or O-butyl (O-C(4)) spacer. It revealed that all newly synthesized compounds were very potent cytotoxic agents against human leukemia and various solid tumors in vitro. These agents did not exhibit cross-resistance against vinblastine-resistant (CCRF-CEM/VBL) or taxol-resistant (CCRF-CEM/taxol) cells. It also showed that these agents were DNA cross-linking agents rather than topoisomerase II inhibitors. Of these agents, compounds 27a and 27c were shown to have potent antitumor activity in nude mice bearing the human breast carcinoma MX-1 xenograft. The therapeutic efficacies of these two agents are comparable to that of taxol.

Answer 14:

Bibliographic Information

DNA adducts formed by a novel antitumor agent 11beta-dichloro in vitro and in vivo. Hillier Shawn M; Marquis John C; Zayas Beatriz; Wishnok John S; Liberman Rosa G; Skipper Paul L; Tannenbaum Steven R; Essigmann John M; Croy Robert G Department of Chemistry and Biological Engineering Division, Massachusetts Institute of Technology, Cambridge, MA 02139, USA Molecular cancer therapeutics (2006), 5(4), 977-84. Journal code: 101132535. ISSN:1535-7163. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) written in English. PubMed ID 16648569 AN 2006241004 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The multifunctional molecule 11beta-dichloro consists of a ligand for the androgen receptor linked to a bifunctional alkylating group, permitting it to create DNA adducts that bind the androgen receptor. We propose that binding of the androgen receptor to 11beta-DNA adducts acts to both shield damaged sites from repair and disrupt the expression of genes essential for growth and survival. We investigated the formation 11beta-DNA adducts in tumor xenograft and nontumor tissues in mice. Using [14C]-11beta-dichloro, we show that the molecule remains intact in blood and is widely distributed in mouse tissues after i.p. injection. Covalent 11beta-guanine adducts identified in DNA that had been allowed to react with 11beta-dichloro in vitro were also found in DNA isolated from cells in culture treated with 11beta-dichloro as well as in DNA isolated from liver and tumor tissues of mice treated with the compound. We used accelerator mass spectrometry to determine the levels of [14C]-11beta-DNA adducts in LNCaP cells treated in culture as well as in liver tissue and LNCaP xenograft tumors in treated mice. The level of DNA adducts in tumor tissue was found to be similar to that found in LNCaP cells in culture treated with 2.5 micromol/L 11beta-dichloro. Our results indicate that 11beta-dichloro has sufficient stability to enter the circulation, penetrate tissues, and form DNA adducts that are capable of binding the androgen receptor in target tissues in vivo. These data suggest the involvement of our novel mechanisms in the antitumor effects of 11beta-dichloro.

Answer 15:

Bibliographic Information

Characterization of a CC49-based single-chain fragment-beta-lactamase fusion protein for antibody-directed enzyme prodrug therapy (ADEPT). Alderson Ralph F; Toki Brian E; Roberge Martin; Geng Wei; Basler Joshua; Chin Regina; Liu Amy; Ueda Roanna; Hodges Douglas; Escandon Enrique; Chen Tianling; Kanavarioti Tessi; Babe Lilia; Senter Peter D; Fox Judith A; Schellenberger Volker Genencor International, a Danisco company, 925 Page Mill Road, Palo Alto, California 94304, USA Bioconjugate chemistry (2006), 17(2), 410-8. Journal code: 9010319. ISSN:1043-1802. (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16536473 AN 2006147849 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

CC49 is a clinically validated antibody with specificity for TAG-72, a carbohydrate epitope that is overexpressed and exposed on the cell surface in a large fraction of solid malignancies. We constructed a single-chain fragment (scFv) based on CC49 and fused it to beta-lactamase (BLA). Following optimization of the scFv domain by combinatorial consensus mutagenesis (CCM) for increased expression and stability, we characterized the protein variant for binding, in vivo pharmacokinetics (PK), and antitumor efficacy. The fusion protein TAB2.5 possessed a similar binding specificity relative to the parent antibody CC49. TAB2.5 also showed prolonged retention (T(1/2) = 36.9 h) in tumor-bearing mice with tumor/plasma ratios of up to 1000. Preliminary evaluation of TAB2.5, in combination with a novel prodrug, GC-Mel, resulted in significant efficacy in a colorectal xenograft tumor model and supports the utility of the protein as an agent for tumor-selective prodrug activation.

Answer 16:

Bibliographic Information

Systemic gene-directed enzyme prodrug therapy of hepatocellular carcinoma using a targeted adenovirus armed with carboxypeptidase G2. Schepelmann Silke; Hallenbeck Paul; Ogilvie Lesley M; Hedley Douglas; Friedlos Frank; Martin Janet; Scanlon Ian; Hay Carl; Hawkins Lynda K; Marais Richard; Springer Caroline J Cancer Research UK Centre for Cancer Therapeutics, Institute of Cancer Research, London, United Kingdom Cancer research (2005), 65(12), 5003-8. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15958540 AN 2005310793 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Hepatocellular carcinoma is the fifth most common cancer worldwide, and there is no effective therapy for unresectable disease. We have developed a targeted systemic therapy for hepatocellular carcinoma. The gene for a foreign enzyme is selectively expressed in the tumor cells and a nontoxic prodrug is then given, which is activated to a potent cytotoxic drug by the tumor-localized enzyme. This approach is termed gene-directed enzyme prodrug therapy (GDEPT). Adenoviruses have been used to target cancer cells, have an intrinsic tropism for liver, and are efficient gene vectors. Oncolytic adenoviruses produce clinical benefits, particularly in combination with conventional anticancer agents and are well tolerated. We rationalized that such adenoviruses, if their expression were restricted to telomerase-positive cancer cells, would make excellent gene vectors for GDEPT therapy of hepatocellular carcinoma. Here we use an oncolytic adenovirus to deliver the prodrug-activating enzyme carboxypeptidase G2 (CPG2) to tumors in a single systemic administration. The adenovirus replicated and produced high levels of CPG2 in two different hepatocellular carcinoma xenografts (Hep3B and HepG2) but not other tissues. GDEPT enhanced the adenovirus-alone therapy to elicit tumor regressions in the hepatocellular carcinoma models. This is the first time that CPG2 has been targeted and expressed intracellularly to effect significant therapy, showing that the combined approach holds enormous potential as a tumor-selective therapy for the systemic treatment of hepatocellular carcinoma.

Answer 17:

Bibliographic Information

Sustained tumor regression of human colorectal cancer xenografts using a multifunctional mannosylated fusion protein in antibody-directed enzyme prodrug therapy. Sharma Surinder K; Pedley R Barbara; Bhatia Jeetendra; Boxer Geoffrey M; El-Emir Ethaar; Qureshi Uzma; Tolner Berend; Lowe Helen; Michael N Paul; Minton Nigel; Begent Richard H J; Chester Kerry A CR UK Targeting and Imaging Group, Department of Oncology, Royal Free and University College Medical School, Royal Free Campus, Rowland Hill Street, London NW3 2PF, United Kingdom. surinder.sharma@ucl.ac.uk Clinical cancer research : an official journal of the American Association for Cancer Research (2005), 11(2 Pt 1), 814-25. Journal code: 9502500. ISSN:1078-0432. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15701872 AN 2005072211 MEDLINE

Abstract

PURPOSE: Antibody-directed enzyme prodrug therapy (ADEPT) requires highly selective antibody-mediated delivery of enzyme to tumor. MFE-CP, a multifunctional genetic fusion protein of antibody and enzyme, was designed to achieve this by two mechanisms. First by using a high affinity and high specificity single chain Fv antibody directed to carcinoembryonic antigen. Second by rapid removal of antibody-enzyme from normal tissues by virtue of post-translational mannosylation. The purpose of this paper is to investigate these dual functions in an animal model of pharmacokinetics, pharmacodynamics, toxicity, and efficacy. EXPERIMENTAL DESIGN: MFE-CP was expressed in the yeast Pichia pastoris and purified via an engineered hexahistidine tag. Biodistribution and therapeutic effect of a single ADEPT cycle (1,000 units/kg MFE-CP followed by 70 mg/kg ZD2767P prodrug at 6, 7, and 8 hours) and multiple ADEPT cycles (9-10 cycles within 21-24 days) was studied in established human colon carcinoma xenografts, LS174T, and SW1222. RESULTS: Selective localization of functional enzyme in tumors and rapid clearance from plasma was observed within 6 hours, resulting in tumor to plasma ratios of 1,400:1 and 339:1, respectively for the LS174T and SW1222 models. A single ADEPT cycle produced reproducible tumor growth delay in both models. Multiple ADEPT cycles significantly enhanced the therapeutic effect of a single cycle in the LS174T xenografts (P = 0.001) and produced regressions in the SW1222 xenografts (P = 0.0001), with minimal toxicity. CONCLUSIONS: MFE-CP fusion protein, in combination with ZD2767P, provides a new and successful ADEPT system, which offers the potential for multiple cycles and antitumor efficacy. These results provide a basis for the next stage in clinical development of ADEPT.

Answer 18:

Bibliographic Information

Potent antitumor N-mustard derivatives of 9-anilinoacridine, synthesis and antitumor evaluation. Bacherikov Valeriy A; Chou Ting-Chao; Dong Hua-Jin; Chen Ching-Huang; Lin Yi-Wen; Tsai Tsong-Jen; Su Tsann-Long Laboratory of Bioorganic Chemistry, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan Bioorganic & medicinal chemistry letters (2004), 14(18), 4719-22. Journal code: 9107377. ISSN:0960-894X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15324894 AN 2004418598 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A series of 9-anilinoacridine N-mustard derivatives, in which the alkylating N-mustard residue was linked to the C-3' or C-4' position of the anilino ring with an O-ethylene spacer, was synthesized and evaluated for cytotoxicity against human lymphoblastic leukemic cells (CCRF-CEM) in culture. The results showed that all of the new compounds exhibited potent cytotoxicity with IC(50) values ranging from 0.002 to 0.7 microM, which were as potent or significantly more potent than 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA). Compound 9 did not exhibit cross-resistance against both vinblastine-resistant (CCRF-CEM/VBL) and taxol-resistant (CCRF-CEM/taxol) cells. Additionally, compound 9 demonstrated potent antitumor effect in nude mice bearing human breast carcinoma MX-1 xenografts, resulting in complete tumor remission in two out of three mice at the maximal dose of 1-2mg/kg (Q3Dx7) or 3mg/kg (Q4Dx5) via intravenous injection.

Answer 19:

Bibliographic Information

Significant differences in biological parameters between prodrugs cleavable by carboxypeptidase G2 that generate 3,5-difluoro-phenol and -aniline nitrogen mustards in gene-directed enzyme prodrug therapy systems. Niculescu-Duvaz I; Scanlon I; Niculescu-Duvaz D; Friedlos F; Martin J; Marais R; Springer C J Cancer Research-UK Centre for Cancer Therapeutics at the Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK Journal of medicinal chemistry (2004), 47(10), 2651-8. Journal code: 9716531. ISSN:0022-2623. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15115406 AN 2004235492 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Nine new nitrogen mustard compounds derived from 2,6-difluoro-4-hydroxy- (3a-e) and 2,6-difluoro-4-amino- (4a-d) aniline were synthesized as potential prodrugs. They were designed to be activated to their corresponding 3,5-difluorophenol and -aniline (4)-nitrogen mustards by the enzyme carboxypeptidase G2 (CPG2) in gene-directed enzyme prodrug therapy (GDEPT) models. The compounds were tested for cytotoxicity in the MDA MB-361 breast adenocarcinoma. The cell line was engineered to express stably either CPG2 tethered to the cell surface stCPG2-(Q)3 or beta-galactosidase (beta-Gal) as control. The cytotoxicity differentials were calculated between CPG 2-expressing and -nonexpressing cells and yielded different results for the two series of prodrugs despite their structural similarities. While the phenol compounds are ineffective as prodrugs, their aniline counterparts exhibit outstanding activity in the tumor cell lines expressing CPG2. [3,5-Difluoro-4-[bis(2-chloroethyl)amino]phenyl]carbamoyl-l-glutamic acid gave a differential of >227 in MDA MB361 cells as compared with 19 exhibited by 4-[(2-chloroethyl)(2-mesyloxyethyl)amino]benzoyl-l-glutamic acid, 1a, which has been in clinical trials.

Answer 20:

Bibliographic Information

Efficient cancer therapy with a nanobody-based conjugate. Cortez-Retamozo Virna; Backmann Natalija; Senter Peter D; Wernery Ullrich; De Baetselier Patrick; Muyldermans Serge; Revets Hilde Department of Molecular and Cellular Interactions, Flanders Interuniversity Institute for Biotechnology, Vrije Universiteit Brussel, Brussels, Belgium

Cancer research (2004), 64(8), 2853-7. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15087403 AN 2004190896 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Nanobodies are the smallest fragments of naturally occurring single-domain antibodies that have evolved to be fully functional in the absence of a light chain. Nanobodies are strictly monomeric, very stable, and highly soluble entities. We identified a nanobody with subnanomolar affinity for the human tumor-associated carcinoembryonic antigen. This nanobody was conjugated to Enterobacter cloacae beta-lactamase, and its site-selective anticancer prodrug activation capacity was evaluated. The conjugate was readily purified in high yields without aggregation or loss of functionality of the constituents. In vitro experiments showed that the nanobody-enzyme conjugate effectively activated the release of phenylenediamine mustard from the cephalosporin nitrogen mustard prodrug 7-(4-carboxybutanamido) cephalosporin mustard at the surface of carcinoembryonic antigen-expressing LS174T cancer cells. In vivo studies demonstrated that the conjugate had an excellent biodistribution profile and induced regressions and cures of established tumor xenografts. The easy generation and manufacturing yield of nanobody-based conjugates together with their potent antitumor activity make nanobodies promising vehicles for new generation cancer therapeutics.

Answer 21:

Bibliographic Information

Synthesis and evaluation of nitroheterocyclic carbamate prodrugs for use with nitroreductase-mediated gene-directed enzyme prodrug therapy. Hay Michael P; Anderson Robert F; Ferry Dianne M; Wilson William R; Denny William A Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand. m.hay@auckland.ac.nz Journal of medicinal chemistry (2003), 46(25), 5533-45. Journal code: 9716531. ISSN:0022-2623. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 14640560 AN 2003569081 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A variety of nitroheterocyclic carbamate prodrugs of phenylenediamine mustard and 5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3H-benz[e]indoline (amino-seco-CBI-TMI), covering a wide range of reduction potential, were prepared and evaluated for use in gene-directed enzyme prodrug therapy (GDEPT) using a two-electron nitroreductase (NTR) from Escherichia coli B. The carbamate prodrugs and corresponding amine effectors were tested in a cell line panel comprising parental and NTR-transfected human (SKOV3/SKOV3-NTR(neo), WiDr/WiDr-NTR(neo)), Chinese hamster (V79(puro)/V79-NTR(puro)), and murine (EMT6/EMT6-NTR(puro)) cell line pairs and were compared with the established NTR substrates CB1954 (an aziridinyl dinitrobenzamide) and the analogous dibromomustard. The 1-methyl-2-nitroimidazol-5-ylmethyl carbamate of phenylenediamine mustard was metabolized rapidly by EMT6-NTR(neo) but not EMT6 cells, demonstrating that it is an efficient substrates for NTR. Despite this, the carbamates of phenylenediamine mustards show relatively low differential cytotoxicity for NTR+ve cells in IC(50) assays, apparently because they retain sufficient alkylating reactivity that most of the prodrug reacts with nucleophiles during the drug exposure period. In contrast, the corresponding amino-seco-CBI-TMI prodrugs were less efficient NTR substrates but had greater chemical stability, were more potent, and showed substantial NTR-ve/NTR+ve ratios in the cell line panel, with ratios of 15-100-fold for the 1-methyl-2-nitro-1H-imidazol-5-ylmethyl and 1-methyl-5-nitro-1H-imidazol-2-ylmethyl carbamates of amino-seco-CBI-TMI. The activity of these two prodrugs was evaluated against NTR-expressing EMT6 tumors comprising ca. 10% NTR+ve cells. Small but not statistically significant killing of NTR+ve cells was observed, with no effect against NTR-ve target cells.

The lack of activity against NTR+ve cells in tumors, despite potent and selective activity in culture, indicates that pharmacokinetic optimization will be required if in vivo efficacy against solid tumors is to be achieved with this new class of NTR prodrugs.

Answer 22:

Bibliographic Information

Measurement of the critical DNA lesions produced by antibody-directed enzyme prodrug therapy (ADEPT) in vitro, in vivo and in clinical material. Webley S D; Francis R J; Pedley R B; Sharma S K; Begent R H; Hartley J A; Hochhauser D Department of Oncology, Royal Free and University College School of Medicine, University College London for the Phase I and II Clinical Trials Committee of the Cancer Research Campaign, UK British journal of cancer (2001), 84(12), 1671-6. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11401322 AN 2001386641 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

An antibody-directed enzyme prodrug therapy (ADEPT) system against CEA-positive tumours is currently in phase I clinical trials. It consists of a prodrug, 4-[N,N-bis(2-iodoethyl) amino] phenoxycarbonyl L -glutamic acid (ZD2767P) and a conjugate of the F(ab')(2) anti-CEA antibody A5B7 and the bacterial enzyme carboxypeptidase G2 (CPG2). ZD2767P is converted by antibody-targeted CPG2 into an active bifunctional alkylating drug (ZD2767) at the tumour site. The IC(50) value of the prodrug against the human colorectal tumour LS174T cell line was 55 +/- 9 microM following a 1 h exposure. In contrast, co-incubation of ZD2767P with CPG2 resulted in 229-fold increase in activity. Using a modified comet assay, DNA interstrand cross links (ISC) were detected within 1 h of ZD2767P + CPG2 treatment and were repaired by 24 h. A clear dose-response was seen between the level of ISC, growth inhibition and ZD2767 concentration. Administration of a therapeutic dose of ZD2767P 72 h after the F(ab')(2) A5B7 conjugate to mice bearing LS147T xenografts resulted in extensive ISC in the tumour after 1 h; repair was seen at 24 h. Tumour biopsies and peripheral lymphocytes were studied in 5 patients on the ADEPT phase I clinical trial. In 4 patients no ISC were detected. These patients also demonstrated poor localization of conjugate and no tumour response was seen. However a significant level of ISC was detected in one tumour biopsy, which also showed evidence of conjugate localization and clinical response. These studies demonstrate the application of the comet assay in the measurement of ISC in vitro and in clinical material and confirm that activation of ZD2767P results in the formation of DNA crosslinks. Copyright 2001 Cancer Research Campaign.

Answer 23:

Bibliographic Information

Regressions of established breast carcinoma xenografts by carboxypeptidase G2 suicide gene therapy and the prodrug CMDA are due to a bystander effect. Stribbling S M; Friedlos F; Martin J; Davies L; Spooner R A; Marais R; Springer C J CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey, United Kingdom Human gene therapy (2000), 11(2), 285-92. Journal code: 9008950. ISSN:1043-0342. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 10680842 AN 2000143035 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The role of the bystander effect in the treatment of a human breast carcinoma xenograft was studied by suicide gene therapy with carboxypeptidase G2 (CPG2) and CMDA. Cells expressing enzymatically active surface-tethered bacterial CPG2 [stCPG2(Q)3] were mixed with control beta-galactosidase (beta-Gal)-expressing cells to give stCPG2(Q)3:beta-Gal ratios of, respectively: group 1, 0:100; group 2, 10:90; group 3, 50:50; and group 4, 100:0. Four days after injection of the cells into nude mice, the prodrug 4-[(2-chloroethyl)(2-mesyloxyethyl)amino]benzoyl-L-glutamic acid (CMDA) was administered. Tumor growth delay correlated well with the levels of stCPG2(Q)3 expression: group 1, 0 day delay; group 2, 10 days; group 3, 16 days; and group 4, 90 days. Similarly, the number of cures was strongly correlated to the levels of stCPG2(Q)3 activity: group 1, zero of six cured; group 2, one of six cured; group 3, three of six cured and group 4, four of six cured. There was a good correlation between CPG2 enzyme activity in the tumors and the number of cures. The majority of cells from groups 2 and 3 were apoptotic whereas those from group 1 were not, indicating a substantial

bystander effect in the tumors. These results suggest that a bystander effect plays a major role in suicide gene therapy regimens with stCPG2(Q)3 and CMDA.

Answer 24:

Bibliographic Information

Enhancement of antibody-directed enzyme prodrug therapy in colorectal xenografts by an antivascular agent. Pedley R B; Sharma S K; Boxer G M; Boden R; Stribbling S M; Davies L; Springer C J; Begent R H Department of Oncology, Royal Free and University College Medical School, University College London, United Kingdom Cancer research (1999), 59(16), 3998-4003. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 10463598 AN 1999391239 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The irregular nature of solid tumor vasculature produces a heterogeneous distribution of antibody-targeted therapies within the tumor mass, which frequently results in reduced therapeutic efficacy. We have, therefore, combined two complementary therapies: Antibody-directed Enzyme Prodrug Therapy (ADEPT), which targets tumor cells, and an agent that selectively destroys tumor vasculature. A single i.p. dose (27.5 mg/kg) of the drug 5,6-dimethylxanthenone-4-acetic acid (DMXAA), given to nude mice bearing the LS174T colorectal xenograft, destroyed all but a peripheral rim of tumor cells, without enhancing survival. The ADEPT system, in which a pretargeted enzyme activates a prodrug, consisted of the F(ab')2 fragment of anti-carcinoembryonic antigen antibody A5B7 conjugated to the bacterial enzyme carboxypeptidase G2 and the prodrug 4-[(2-chloroethyl)(2-mesyloxyethyl)amino]benzoyl-L-glutamic acid, which was given i.p. in three doses of 500 mg/kg at 72, 84, and 96 h post-conjugate administration (25 units of carboxypeptidase G2). The antibody-enzyme conjugate could be selectively retained at approximately twice the control levels by administration of the antivascular agent at the time of optimal conjugate localization within the tumor (20 h post-conjugate administration), as demonstrated by gamma counting, phosphor plate image analysis, and active enzyme measurement. This resulted in significantly enhanced tumor growth inhibition in groups of six mice, compared to conventional ADEPT therapy, with no concomitant increase in systemic toxicity. In a separate experiment, aimed at trapping the prodrug within the tumor, a 16-fold increase over control values was produced (means, 44.8 versus 2.8 microg/g tumor) when DMXAA was given 4 h prior to 4-[(2-chloroethyl)(2-mesyloxyethyl)amino]benzoyl-L-glutamic acid. The therapeutic window was small, with no significant enhancement of prodrug retention when DMXAA was given at either earlier or later time points.

This correlated with the time of vascular shut-down induced by the antivascular agent. We are currently investigating whether it is more advantageous to trap increased levels of conjugate or prodrug within the tumor for maximal enhancement of conventional ADEPT. These studies demonstrate that combined use of antibody-directed and antivascular therapies can significantly benefit the therapeutic outcome of either strategy alone.

Answer 25:

Bibliographic Information

Tallimustine, an effective antileukemic agent in a severe combined immunodeficient mouse model of adult myelogenous leukemia, induces remissions in a phase I study. Beran M; Jeha S; O'Brien S; Estey E; Vitek L; Zurlo M G; Rios M B; Keating M; Kantarjian H Leukemia Department, Division of Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA Clinical cancer research : an official journal of the American Association for Cancer Research (1997), 3(12 Pt 1), 2377-84. Journal code: 9502500. ISSN:1078-0432. (CLINICAL TRIAL); (CLINICAL TRIAL, PHASE I); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 9815637 AN 1999111195 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Despite progress in leukemia therapy, only 20-30% of patients with acute myelogenous leukemia (AML) are cured. 1-beta-D-arabinofuranosylcytosine- and topoisomerase II-reactive drugs are the primary therapeutic agents used. The aim of this study was to evaluate the potential activity of tallimustine in leukemia. In this study, we first investigated the efficacy and toxic effects of tallimustine, a distamycin-A derivative, in a human leukemia model in severe combined immunodeficient (SCID) mice. On the basis of its dramatic activity in this preclinical study, a Phase I study of tallimustine at a starting dose of 300 microgram/m2/day for 3 days every 3-4 weeks was conducted in patients with refractory or relapsed leukemia. In SCID mice grafted with a human myelomonocytic leukemia cell line, tallimustine resulted in complete remission of disease in most mice at tolerable dosages ranging from 0.86 to 3.0 mg/kg/day for 3 days and was combined effectively and safely with a 2-day schedule of high-dose ara-C. In the Phase I study, 26 patients with refractory or relapsed leukemia were treated. The maximum tolerated dose was 900 microgram/m2/day for 3 days every 3-4 weeks. This dose was 3 times higher than the maximum tolerated dose in solid tumors and was limited by severe mucositis. Magnesium and potassium wasting were also observed, but other side effects (fatigue and gastrointestinal) were minor. Two (8%) patients with AML achieved complete remission and two achieved hematological improvement with persistent thrombocytopenia. The results of this study indicate that tallimustine has promising activity in AML. Future studies may combine tallimustine with other agents known to be active against AML, and investigate its activity in other hematological malignancies. The recommended Phase II single-agent dose of tallimustine is 750-900 microgram/m2/day for 3 days, and combination studies may start at 50-66% of this dose schedule.

The SCID mouse model of human leukemia may be promising in the preclinical evaluation and selection of potential antileukemic agents.

Answer 26:

Bibliographic Information

Tumor efficacy and bone marrow-sparing properties of TER286, a cytotoxin activated by glutathione S-transferase. Morgan A S; Sanderson P E; Borch R F; Tew K D; Niitsu Y; Takayama T; Von Hoff D D; Izbicka E; Mangold G; Paul C; Broberg U; Mannervik B; Henner W D; Kauvar L M Terrapin Technologies, Inc., South San Francisco, California 94080, USA Cancer research (1998), 58(12), 2568-75. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9635580 AN 1998297503 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

TER286 is a latent drug activated by human glutathione S-transferase (GST) isoforms P1-1 and A1-1 to produce a nitrogen mustard alkylating agent. M7609 human colon carcinoma, selected for resistance to doxorubicin, and MCF-7 human breast carcinoma, selected for resistance to cyclophosphamide, both showed increased sensitivity to TER286 over their parental lines in parallel with increased expression of GST P1-1. In primary human tumor clonogenic assays, the spectrum of cytotoxic activity observed for TER286 was both broad and unusual when compared to a variety of current drugs. In murine xenografts of M7609 engineered to have high, medium, or low GST P1-1, responses to TER286 were positively correlated with the level of P1-1. Cytotoxicity was also observed in several other cell culture and xenograft models. In xenografts of the MX-1 human breast carcinoma, tumor growth inhibition or regression was observed in nearly all of the animals treated with an aggressive regimen of five daily doses. This schedule resulted in a 24-h posttreatment decline in bone marrow progenitors to 60% of control and was no worse than for a single dose of TER286. These studies have motivated election of TER286 as a clinical candidate.

Answer 27:

Bibliographic Information

A cell surface tethered enzyme improves efficiency in gene-directed enzyme prodrug therapy. Marais R; Spooner R A; Stribbling S M; Light Y; Martin J; Springer C J CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey, UK Nature biotechnology (1997), 15(13), 1373-7. Journal code: 9604648. ISSN:1087-0156. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English.

PubMed ID 9415889 AN 1998077738 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The potential for expressing the bacterial enzyme carboxypeptidase G2 (CPG2) tethered to the outer surface of mammalian cells was examined for use in gene-directed enzyme prodrug therapy. The affinity of CPG2 for the substrate methotrexate was unaffected by three mutations required to prevent N-linked glycosylation. Breast carcinoma MDA MB 361 cells expressing CPG2 internally showed only a very modest increase in sensitivity to the prodrug CMDA because the prodrug did not enter the cells. Cells expressing surface-tethered CPG2, however, became 16-24-fold more sensitive to CMDA and could mount a good bystander effect. Systemic administration of CMDA to mice bearing established xenografts of the transfected cells led to sustained tumor regressions or cures.

Answer 28:

Bibliographic Information

Cytotoxic and antitumor activity of MEN 10710, a novel alkylating derivative of distamycin. Bigioni M; Salvatore C; Palma C; Manzini S; Animati F; Lombardi P; Pratesi G; Supino R; Zunino F Pharmacology Department, Menarini Ricerche, Pomezia (Rome), Italy Anti-cancer drugs (1997), 8(9), 845-52. Journal code: 9100823. ISSN:0959-4973. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9402311 AN 1998063903 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

MEN 10710 is a new synthetic distamycin derivative possessing four pyrrole rings and a bis-(2-chloroethyl)aminophenyl moiety linked to the oligopyrrole backbone by a flexible butanamido chain. Its biological properties have been investigated in comparison with the structurally related compound, tallimustine (FCE24517), and the classical alkylating agent, melphalan (L-PAM). Cytotoxic potency of MEN 10710 was increased from 10- to 100-fold, as compared to tallimustine or L-PAM in murine L1210, human LoVo and MCF7 tumor cell lines. MEN 10710 was still active against L1210/L-PAM leukemic cells, while a partial cross-resistance was observed in LoVo/DX and in MCF7/DX cells selected for resistance to doxorubicin and expressing a MDR phenotype. Treatment with verapamil (VRP) reduced the resistance to tallimustine, but not to MEN 10710, in MCF7/DX cells. The cytotoxic effects reflect in vivo antitumor potency and toxicity in the treatment of human tumor xenografts. MEN 10710 was more effective in A2780/DDP, an ovarian carcinoma selected for resistance to cisplatin. On the other hand, the IC30 for inhibiting murine granulocyte/macrophage colony formation was 50 times higher for MEN 10710 than for tallimustine, suggesting a lower myelotoxic potential. In conclusion, the particular biological profile of MEN 10710 characterized by a marked cytotoxic potency, an interesting antitumor efficacy and a reduced in vitro myelosuppressive action may represent a further improvement in the rational design of a novel distamycin-related alkylating compound.

Answer 29:

Bibliographic Information

Biodistribution of an antibody-enzyme conjugate for antibody-directed enzyme prodrug therapy in nude mice bearing a human colon adenocarcinoma xenograft. Stribbling S M; Martin J; Pedley R B; Boden J A; Sharma S K; Springer C J CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey, UK Cancer chemotherapy and pharmacology (1997), 40(4), 277-84. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9225945 AN 1997369457 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The enzyme carboxypeptidase G2 (CPG2) can be targeted to tumors by antibodies and used to activate prodrugs in a treatment called antibody-directed enzyme prodrug therapy (ADEPT). Different doses of CPG2 conjugated to the anti-CEA antibody A5B7 were administered i.v. to nude mice bearing the LS174T human colon adenocarcinoma xenograft, and the biodistribution of conjugate activity 48 and 72 h later was determined using a novel high-performance liquid chromatography (HPLC) method. Conjugate doses of 2,500 and 625 U/kg gave tumor enzyme levels of 0.5-0.6 U/g. Lower doses of 300 and 150 U/kg gave tumor enzyme levels of 0.1-0.3 U/g. Intriguingly, the best tumor:blood ratio of conjugate activity at both 48 and 72 h was achieved after administration of the 625-U/kg dose, not the 2,500-U/kg dose. After 48 h this ratio was 3.8, whereas after 72 h the value was 5.5. This conjugate dose also gave the greatest tumor:tissue ratios in all other tissues examined. After 72 h the tumor:colon ratio was 105, whereas the tumor:kidney ratio was 36. In ADEPT, to obtain maximal tumor damage to LS174T xenografts in nude mice with minimal systemic toxicity using the A5B7-CPG2 conjugate, prodrug should therefore be administered at least 72 h after a conjugate dose of 625 U/kg.

Answer 30:

Bibliographic Information

ZD2767, an improved system for antibody-directed enzyme prodrug therapy that results in tumor regressions in colorectal tumor xenografts. Blakey D C; Burke P J; Davies D H; Dowell R I; East S J; Eckersley K P; Fitton J E; McDaid J; Melton R G; Niculescu-Duvaz I A; Pinder P E; Sharma S K; Wright A F; Springer C J Cancer, Metabolism, and Endocrine Research Department, Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, United Kingdom Cancer research (1996), 56(14), 3287-92. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8764123 AN 1996320473 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

ZD2767 represents an improved version of antibody-directed enzyme prodrug therapy. It consists of a conjugate of the F(ab')2 A5B7 antibody fragment and carboxypeptidase G2 (CPG2) and a prodrug, 4-[N,N-bis(2-iodoethyl)amino]phenoxycarbonyl L-glutamic acid. The IC50 of the prodrug against LoVo colorectal tumor cells was 47 microM, and cleavage by CPG2 released the potent bis-iodo phenol mustard drug (IC50 = 0.34 microM). The drug killed both proliferating and quiescent LoVo cells. Administration of the ZD2767 conjugate to nude mice bearing LoVo colorectal xenografts resulted in approximately 1% of injected ZD2767 conjugate localizing/g of tumor after 72 h, and blood and normal tissue levels of the conjugate were 10-50-fold lower. A single round of therapy involving the administration of the prodrug 72 h after the conjugate to athymic mice bearing established LoVo xenografts resulted in approximately 50% of the tumors undergoing complete regressions, tumor growth delays greater than 30 days, and little toxicity (as judged by body-weight loss). Similar studies using a control antibody-CPG2 conjugate that does not bind to LoVo tumor cells resulted in a growth delay of less than 5 days, confirming the tumor specificity of this approach. These studies demonstrate the potential of ZD2767 for the treatment of colorectal cancer.

Answer 31:

Bibliographic Information

Regressions and cures of melanoma xenografts following treatment with monoclonal antibody beta-lactamase conjugates in combination with anticancer prodrugs. Kerr D E; Schreiber G J; Vrudhula V M; Svensson H P; Hellstrom I; Hellstrom K E; Senter P D Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121, USA Cancer research (1995), 55(16), 3558-63. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7627964 AN 1995354147 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Cephalosporin doxorubicin (C-Dox) and 7-(4-carboxybutanamido)-cephalosporin mustard (CCM) are prodrugs that are catalytically converted by Enterobacter cloacae beta-lactamase (bL) to the active anticancer agents doxorubicin and phenylenediamine mustard, respectively. Both prodrugs were less cytotoxic to the 3677 human melanoma line than their respective drugs and were activated in an immunologically specific manner by 96.5-bL, a mAb-bL conjugate that binds to 3677 cell surface antigens. Similar results were obtained using the CCM prodrug on SK-MEL 28 human melanoma cells. Experiments in mice with established s.c. 3677 tumors demonstrated that although no tumors were cured in mice receiving the 96.5-bL/C-Dox combination, the activities were greater than those obtained from systemic doxorubicin treatment or from administration of the nonbinding conjugate P1.17-bL in combination with C-Dox. In contrast, when CCM was used as a prodrug, cures of established 3677 tumors were obtained in 80% of the 96.5-bL treated animals. This combination was also able to induce regressions of large 3677 tumor masses (800 mm3) without any apparent toxic side effects. We conclude that 96.5-bL in combination with C-Dox or CCM has greater antitumor activity than systemic treatment with the corresponding drugs and that CCM is a more effective prodrug than C-Dox for treating human 3677 melanoma xenografts.

Answer 32:

Bibliographic Information

Antitumor effects of an antibody-carboxypeptidase G2 conjugate in combination with a benzoic acid mustard prodrug. Blakey D C; Valcaccia B E; East S; Wright A F; Boyle F T; Springer C J; Burke P J; Melton R G; Bagshawe K D ICI Pharmaceuticals, Macclesfield, Cheshire Cell biophysics (1993), 22(1-3), 1-8. Journal code: 8002185. ISSN:0163-4992. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7889535 AN 1995196228 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The F(ab')2 fragment of the antitumor monoclonal antibody, A5B7, was covalently linked to the bacterial enzyme carboxypeptidase G2 (CPG2). The resulting conjugate was used in combination with a prodrug of a benzoic acid mustard alkylating agent to treat human colon tumor xenografts in a two-step targeting strategy, antibody-directed enzyme prodrug therapy (ADEPT). The prodrug, 4-[(2-chloroethyl) (2-mesyloxyethyl)amino]-benzoyl-L-glutamic acid is rapidly converted by CPG2 to a drug that is at least 15x more toxic in vitro against LS174T colorectal tumor cells than the prodrug. Optimal tumor/blood ratios of the A5B7-CPG2 were achieved 72 h after administration of the conjugate to athymic mice bearing established LS174T tumor xenografts. Significant antitumor activity was seen in LS174T tumor-bearing mice treated with the conjugate followed 3 d later by the prodrug. In contrast, prodrug, conjugate, or active drug alone did not result in any antitumor activity in this tumor model. These studies demonstrate the advantage of a two-step ADEPT system for the treatment of colorectal cancer.

Answer 33:

Bibliographic Information

Antibody directed enzyme prodrug therapy (ADEPT): clinical report. Bagshawe K D; Sharma S K; Springer C J; Antoniw P; Boden J A; Rogers G T; Burke P J; Melton R G; Sherwood R F Department of Medical Oncology, Charing Cross and Westminster Medical School, London Disease markers (1991), 9(3-4), 233-8. Journal code: 8604127. ISSN:0278-0240. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 1813213 AN 1992257856 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Following an extensive series of studies in nude mice with human xenografts a pilot scale clinical trial of antibody directed enzyme prodrug therapy has been initiated. The principle is to activate a relatively inert prodrug to an active cytotoxin by

a tumour located enzyme. In the first stage of the study a prodrug para-N-(mono-2-chloroethyl monomesyl)-aminobenzoyl glutamic acid was administered to six patients with advanced colorectal cancer in a dose escalating protocol. Nausea and vomiting occurred as the only discernible toxic effect at the higher dose levels. Three of these patients and two other patients with advanced disease have proceeded to the second stage of the study in which an antibody-enzyme conjugate was given IV, followed after 36-48 h by a galactosylated anti-enzyme antibody. When plasma enzyme levels had become undetectable the patients received multiple doses of the prodrug. At the lower doses toxicity was minimal as were clinical responses. Two patients received higher doses which resulted in myelosuppression and temporary regression of advanced disease. No complications resulted from administration of the antibody-enzyme complex or enzyme inactivating antibody. The myelosuppression is attributable to the relatively long half-life of the active drug formed from the prodrug used in the present study.

Answer 34:

Bibliographic Information

Biological profile of FCE 24517, a novel benzoyl mustard analogue of distamycin A. Pezzoni G; Grandi M; Biasoli G; Capolongo L; Ballinari D; Giuliani F C; Barbieri B; Pastori A; Pesenti E; Mongelli N; + Farmitalia Carlo Erba, Research Center, Erbamont Group, Milano, Italy British journal of cancer (1991), 64(6), 1047-50. Journal code: 0370635. ISSN:0007-0920. (IN VITRO); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1764367 AN 1992110172 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

FCE 24157 (chemically (beta-[1-methyl-4-(1-methyl-4--[1-methyl-4-(4-N,N- bis(2-chloroethyl) amino-benzene-1-carboxy-amido) pyrrole-2-carboxiamido]pyrrole-2-carboxyamido)pyrrole-2-c arboxyamido]) propionamidine, hydrochloride) is a distamycin A (Dista A) derivative bearing a benzoyl mustard moiety instead of the formyl group at the N-terminal. Contrary to Dista A, FCE 24517 has been found to display potent cytotoxic activity on human and murine tumour cell lines. The compound maintains activity on melphalan (L-PAM)-resistant cells, whereas cross-resistance is observed on doxorubicin-(DX)-resistant cells. In vivo, FCE 24517 was found to possess evident antineoplastic activity on a series of murine transplanted solid tumours and human tumour xenografts. The following neoplasms were in fact found to be sensitive to FCE 24517 treatment: M14 human melanoma xenograft, N592 human small cell lung carcinoma, MTV murine mammary carcinoma, Colon 38 murine carcinoma, PO2 murine pancreatic carcinoma and M5076 murine reticulosarcoma. Lower effectiveness was observed against the murine P388 and Gross leukaemia, Lewis lung murine carcinoma, LoVo human colon carcinoma xenografts and A459 human lung adenocarcinoma. Against the murine L1210 leukaemia, FCE 24517 displayed a clear activity only when the tumour was transplanted i.p. and treatment was given i.p., whereas only marginal activity was seen against this leukaemia if transplanted i.v. and the drug was given i.v. As true also in vitro, FCE 24517 was effective against i.p. implanted L1210 leukaemia resistant to L-PAM. The mode(s) of action of this new compound is under active investigation.

Answer 35:

Bibliographic Information

Disposition of the prodrug 4-(bis (2-chloroethyl) amino) benzoyl-L-glutamic acid and its active parent drug in mice. Antoniw P; Springer C J; Bagshawe K D; Searle F; Melton R G; Rogers G T; Burke P J; Sherwood R F Department of Medical Oncology, Charing Cross Hospital, London, UK British journal of cancer (1990), 62(6), 909-14. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2257218 AN 1991077259 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A novel therapy for improving selectivity in cancer chemotherapy aims to modify distribution of a cytotoxic drug by generating it selectively at tumour sites. In this approach an antibody-enzyme conjugate is allowed to localise at the tumour sites before injecting a prodrug which is converted to an active drug specifically by the targeted enzyme in the conjugate. We present here pharmacokinetic studies on the prodrug 4-(bis (2-chloroethyl) amino) benzoyl-L-glutamic acid and its activated derivative, benzoic acid mustard. The glutamic acid is cleaved from the prodrug to form the active drug by carboxypeptidase G2 (CPG2), an enzyme from Pseudomonas sp., which is not found in mammalian cells. The prodrug and its parent active drug were rapidly distributed in plasma and tissues after administration of prodrug or active drug (41 mumol kg-1 intraperitoneally) to mice bearing human choriocarcinoma xenografts. Prodrug and active drug both followed a two-compartment kinetic model. Prodrug was eliminated more rapidly (t1/2 alpha = 0.12 h, t1/2 beta = 0.70 h) than active drug (t1/2 alpha = 0.37 h, t1/2 beta = 1.61 h). Conversion of the prodrug to the activated parent drug was detected within 5 min of administration to mice which had previously received a F(ab')2-anti-human chorionic gonadotrophin antibody (W14A) conjugated to the enzyme, CPG2 (1,000 U kg-1). Tumour was the only tissue that activated all the prodrug reaching the site. It contained the highest concentration of targeted enzyme conjugate capable of catalysing the reaction of prodrug to drug. Plasma and other tissues were also capable of activating the prodrug but active drug production was limited by the amount of enzyme present. The active drug measured in plasma and tissues other than tumour was attributable to residual antibody-enzyme conjugate at non-tumour sites. Low levels of conjugate in tissues and plasma militate against the advantage of tumour localised enzyme therefore necessitating removal of non-localised enzyme.

Answer 36:

Bibliographic Information

In vitro and in vivo anticancer activity of mitozolomide and sparsomycin in human tumor xenografts, murine tumors and human bone marrow. Fiebig H H; Berger D P; Kopping K; Ottenheijm H C; Zylicz Z Department of Internal Medicine, University of Freiburg, Federal Republic of Germany Journal of cancer research and clinical oncology (1990), 116(6), 550-6. Journal code: 7902060. ISSN:0171-5216. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2254373 AN 1991072450 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The colony formation in agar of human tumor xenografts, of murine tumors and of human bone marrow was used as a test system to determine the in vitro activity of the two novel cytostatic agents, mitozolamide and sparsomycin. Mitozolomide was additionally studied in vivo in nine human tumor xenografts. The comparison of in vitro/in vivo activity allows an assessment of the relevant in vitro dose based on in vivo pharmacological behavior of a compound. Both compounds showed clear dose/response effects in vitro. A dose of 3 micrograms/ml mitozolomide, given by continuous exposure, was active (colony number of test less than 30% of the control group) in 12/42 (29%) human tumor xenografts as well as in the four murine tumors, P388, L1210, B16 melanoma and colon carcinoma 38, whereas the two human bone marrows showed no significant suppression of the ability to form colonies in culture. The comparison of in vitro with in vivo activity suggests that the in vitro dose of 3 micrograms/ml corresponds best to the activity observed in animal experiments. The highest activity was observed in small-cell cancer of the lung (4/5), followed by melanomas (2/7) and non-small-cell cancer of the lung (2/9). Furthermore, activity was found in a cancer of the large bowel, stomach, breast and in one sarcoma. In the treatment of nine human tumor xenografts growing subcutaneously in nude mice, mitozolomide effected a complete or partial remission in 6 out of 9 tumors. In comparison to standard drugs mitozolomide is one of the most effective compounds in these tumors. These data indicate that mitozolomide possesses potent broad-spectrum activity in human tumor xenografts. Sparsomycin (0.1 micrograms/ml, continuous exposure) was active in 11/46 (24%) human tumor xenografts and in 4/5 of the murine tumors, whereas the colony-forming capacity of four human bone-marrows showed no inhibition, suggesting that this dose level may be the relevant in vitro dose.

However, the high in vitro activity in murine tumors is incompatible with the in vivo activity. In mice the only responsive tumor was leukemia P388, whereas the L1210, B16 melanoma and colon carcinoma 38 were resistant. At the dose level of 0.03 microgram/ml only 3/30 (10%) of the human tumor xenografts were sensitive. In an earlier clinical phase I study the dose-limiting adverse effect was eye toxicity and not bone-marrow suppression.(ABSTRACT TRUNCATED AT 400 WORDS)

Answer 37:

Bibliographic Information

A human tumor lung metastasis model in athymic nude rats. Kjonniksen I; Storeng R; Pihl A; McLemore T L; Fodstad O Department of Tumor Biology, Norwegian Radium Hospital, Oslo Cancer research (1989), 49(18), 5148-52. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2766284 AN 1989354292 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Experimental lung metastases regularly developed in athymic Han:rnu/rnu Rowett rats after i.v. injection of LOX human malignant melanoma cells. When 5 x 10(5) tumor cells were injected into 4-week-old rats, 89% of the animals died of lung tumors, with a mean survival time of 18 days. With 5- and 6-week-old rats, however, the fraction of animals that died decreased to 80 and 46%, with mean survival times of 35 and 38 days, respectively. The number of detectable lung colonies in each animal was about 35 in 5- and 6-week-old animals, compared to nearly 300 in 4-week-old rats. In the latter, a correlation was found between the number of tumor cells injected and the number of detectable lung colonies. The capacity of the LOX tumor to grow s.c. and to form experimental lung metastases was, by and large, similar in young nude rats and in nude mice, and no significant difference in morphology between the different tumors in the two species was seen. A high-resolution radiographic method was used to visualize lung colonies in the nude rats, and single tumors with diameters as small as 2-4 mm could be detected. By this method, for the first time, the effect of chemotherapy on a human tumor growing in a visceral organ of a rodent host could be followed by repeat X-ray examinations, mimicking a situation commonly faced in the clinic. This procedure may prove particularly useful for experimental chemotherapy studies, and may be extended to other human tumors that frequently metastasize to the lungs. Indications were obtained that some host-specific differences in tissue-preferenced growth might exist, a possibility that will be further explored.

Answer 38:

Bibliographic Information

A cytotoxic agent can be generated selectively at cancer sites. Bagshawe K D; Springer C J; Searle F; Antoniw P; Sharma S K; Melton R G; Sherwood R F Department of Medical Oncology, Charing Cross Hospital, London, UK British journal of cancer (1988), 58(6), 700-3. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3265633 AN 1989134666 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Attempts to improve the selectivity of anti-cancer agents by conjugating them to antibodies directed at tumour associated antigens have demonstrated tumour localisation but only limited therapeutic success. We report here the advantage of a 2-stage approach in which the first component combines the selective delivery of antibody with a capability to generate a cytotoxic agent from a second subsequently administered component. A bacterial enzyme, carboxypeptidase G2 (CPG2) was conjugated with F(ab')2 fragment of a monoclonal antibody directed at beta subunit of human chorionic gonadotrophin (beta-hCG) and injected into nude mice bearing hCG producing CC3 xenografts of human choriocarcinoma. Time was allowed for the conjugate to localise at tumour sites and clear from blood before injecting para-N-bis (2-chloroethyl) aminobenzoylglutamic acid. Cleavage of the glutamic acid moiety from this molecule by CPG2 released a benzoic acid mustard. Growth of the tumour which is resistant to conventional chemotherapy was markedly depressed by a single course of treatment. This demonstrates for the first time the potential of an antibody directed enzyme to activate an alkylating agent and to eradicate an established human cancer xenograft.

Answer 39:

Bibliographic Information

Evaluation of 3-(p-fluorophenyl)-L-alanyl-3-[m-bis-(2-chloroethyl) aminophenyl]-L-alanyl-L-methionine ethyl ester HCl (PTT.119) against xenografts of human rhabdomyosarcoma. Houghton P J; Tharp R; Houghton J A; Holland J F; Bekesi J G Laboratories for Developmental Therapeutics, St. Jude Children's Research Hospital, Memphis, Tennessee 38101 Cancer chemotherapy and pharmacology (1988), 22(3), 201-4. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 3409455 AN 1988311349 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PTT.119 [p-F-phe-m-bis(2-chloroethyl)amino-L-phe-met ethoxy HCl], a synthetic tripeptide mustard, was evaluated for therapeutic efficacy against a spectrum of childhood rhabdomyosarcomas (RMS) maintained as xenografts in immune-deprived mice. These xenografts were established from previously untreated tumors, and sublines were selected in mice for resistance to L-phenylalanine mustard (L-PAM). PTT.119 caused regression of four of six RMS lines established from untreated tumors, and demonstrated activity similar to that of L-PAM in this model. Against tumors Rh18/L-PAM and Rh28/L-PAM, selected in situ for L-PAM resistance, PTT.119 had no significant activity. Rh28/L-PAM was cross-resistant also to oxazophosphorine mustards (ifosfamide, cyclophosphamide), and both tumors were cross-resistant to adriamycin and vincristine. PTT.119 caused hematologic toxicity similar to that of L-PAM, characterized by a marked decrease in white blood cells and thrombocytopenia.

Answer 40:

Bibliographic Information

Phase II testing of melphalan in children with newly diagnosed rhabdomyosarcoma: a model for anticancer drug development. Horowitz M E; Etcubanas E; Christensen M L; Houghton J A; George S L; Green A A; Houghton P J Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN Journal of clinical oncology : official journal of the American Society of Clinical Oncology (1988), 6(2), 308-14. Journal code: 8309333. ISSN:0732-183X. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 3276826 AN 1988117656 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We describe events that led to successful testing of melphalan, one of the nitrogen mustard compounds, in children with newly diagnosed, poor-risk rhabdomyosarcoma (RMS). Preclinical studies with xenografts of human RMS, growing in the flanks of immune-deprived mice, had indicated superior oncolytic activity by melphalan compared with other agents commonly used to treat this tumor. However, in a conventional phase II trial, melphalan failed to produce partial responses in 12 of 13 heavily pretreated patients with recurrent tumors. Subsequent comparison of the drug's pharmacokinetics in mice and patients indicated that its poor clinical performance was not the result of interspecies differences in drug disposition. Therefore, we elected to retest melphalan in untreated patients, before they were enrolled in a phase III study. Of 13 children who received the drug for 6 weeks, ten had partial responses, confirming the significant antitumor activity seen in the xenograft system. These findings illustrate the inherent limitations of phase II drug trials in previously treated patients and suggest a useful paradigm for the development of antineoplastic drugs.

Answer 41:

Bibliographic Information

Activity and distribution studies of etoposide and mitozolomide in vivo and in vitro against human choriocarcinoma cell lines. Brindley C J; Pedley R B; Antoniw P; Newlands E S Cancer chemotherapy and pharmacology (1987), 19(3), 221-5. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3581415 AN 1987216393 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The in vivo antitumor activity of etoposide and mitozolomide was assessed in nude mice bearing a xenograft (CC3) of human gestational choriocarcinoma. Both agents demonstrated, at best, marginal activity observed as a delay in tumour growth. This lack of sensitivity suggests that the CC3 xenograft is not a good model for selection of agents for clinical evaluation in gestational choriocarcinoma. Plasma and tissue concentrations of etoposide and mitozolomide were measured in nude mice. Drug concentrations found in tumour tissue were 60% and 30% of plasma levels for mitozolomide and etoposide respectively. Etoposide and mitozolomide activity was also evaluated in vitro with another choriocarcinoma cell line (JAR). Maximum cell-kill was achieved after exposure to etoposide 0.05-1 microgram/ml for 3-24 h. In vitro response to etoposide demonstrates the importance of exposure time in determining cytotoxicity. In contrast, mitozolomide at concentrations from 1-100 micrograms/ml did not have a marked effect against JAR after exposure for 3-24 h.

Answer 42:

Bibliographic Information

Activity of mitozolomide (NSC 353451), a new imidazotetrazine, against xenografts from human melanomas, sarcomas, and lung and colon carcinomas. Fodstad O; Aamdal S; Pihl A; Boyd M R Cancer research (1985), 45(4), 1778-86. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 3978640 AN 1985151834 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The chemosensitivity of human tumor xenografts to mitozolomide, 8-carbamoyl-3-(2-chloroethyl)imidazo[5-1-d]-1,2,3,5-tetrazin-4(3H) -one, was studied in 3 different assay systems. In concentrations of 1 to 500 micrograms/ml, mitozolomide completely inhibited the colony-forming ability in soft agar of cell suspensions from sarcomas, melanomas, lung and colon cancers, and a mammary carcinoma. When a panel of tumors of the different histological types was tested for its sensitivity to mitozolomide in vitro, in the 6-day subrenal capsule assay in conventional mice, and, in some cases, as s.c. growing tumors in nude mice, good agreement between the different assay systems was seen. In most cases, a very pronounced antitumor effect was observed. The efficacy of mitozolomide was as good or better than that of the drugs clinically used against the tumor types tested. Tumor size measurements and histological examinations indicated that nude mice carrying a melanoma, a small cell lung cancer, and an osteosarcoma were cured of their tumors. The approach here used for evaluating the effect of a new drug on human cancers may be useful for selecting the tumor types which primarily should be studied in clinical trials. The results indicate that clinical responses to mitozolomide may be anticipated in sarcoma, melanoma, small cell lung cancer, and possibly in colon cancer.

Answer 43:

Bibliographic Information

Further studies on the anti-neoplastic activity of 3 beta-hydroxy-13 alpha-amino-13,17-seco-5 alpha-androstan-17-oic-13,17-lactam [p-[bis(2-chloroethyl)amino]-phenyl]acetate (NSC 290205). Catsoulacos P Cancer letters (1984), 22(2), 199-202. Journal code: 7600053. ISSN:0304-3835. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 6704948 AN 1984156227 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The modified steroidal alkylating agent 3 beta-hydroxy-13 alpha-amino-13,17-seco-5 alpha-androstan-17-oic-13,17-lactam [p-[bis(2-chloroethyl)amino]phenyl]acetate (NSC 290205) is active in treating the LX-1 lung and MX-1 breast xenografts as well as a number of rodent tumors. Of 13 tumors tested, activity has been shown in 10 systems. Two systems have not received adequate testing and negative results were recorded in 1 system.

Answer 44:

Bibliographic Information

Response of a high-glucuronidase human tumour xenograft to aniline mustard. Warenius H M; Workman P; Bleehen N M British journal of cancer (1982), 45(1), 27-34. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 7059462 AN 1982135269 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The HT29R colonic adenocarcinoma xenograft has been shown to be rich in the enzyme beta-glucuronidase. Experiments in rodent systems have demonstrated a marked anti-tumour effect of the drug aniline mustard (AM) on tumours with high levels of this enzyme (e.g. the plasmacytomas PC5 and PC6). We have found that AM is no more effective than its analogue paramethyl aniline mustard (PMAM) or other alkylating agents against the HT29R xenograft. Amongst the possible explanations for this may be: (1) The wide shoulder on the cell-survival curve shown for exposure to alkylating agents of HT29R in vivo. (2) Lack of correlation between physiological availability of beta-glucuronidase and the high levels measured by the standard assay. (3) Increased beta-glucuronidase levels in host mouse marrow, making the latter potentially more susceptible to AM damage.

Answer 45:

Bibliographic Information

The immunosuppressive effect of beta-[1-phenyl-5-bis(beta-chloroethyl)-aminobenzimidazolyl-(2)]-DL-alanine (ZIMET 3164) on cell-mediated immunity in mice. Heinecke H; Ozegowski W Allergie und Immunologie (1980), 26(1), 41-5. Journal code: 0314702. ISSN:0323-4398. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 6447447 AN 1980262822 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The potential immunosuppressive drug beta-[1-Phenyl-5-bis(beta-chloroethyl-5-amino-benzimidazolyl-(2)]-DL-alanine (ZIMET 3164) was tested for its effect on cell-mediated immunity. The models "skin grafting" and "contact hypersensitivity" were used. --The results showed a marked prolongation of the mean survival time of the skin grafts and also a high depression of the contact hypersensitivity (delayed hypersensitivity) to picryl chloride. The immunosuppressive efficacy of ZIMET 3164 was higher than that of the reference compound cyclophosphamide.

Answer 46:

Bibliographic Information

The sensitivity to chemotherapeutic agents of a rat tumour grown in immunosuppressed mice. Sheard C E; Double J A; Berenbaum M C British journal of cancer (1971), 25(4), 838-44. Journal code: 0370635. ISSN:0007-0920. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 5144544 AN

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